

**WHAT IS CLAIMED IS:**

1. A composition comprising a first oligomeric compound and a second oligomeric compound wherein:

at least a portion of the first oligomeric compound is capable of hybridizing with at least  
5 a portion of the second oligomeric compound;

at least a portion of the first oligomeric compound is complementary to and capable of hybridizing to a target nucleic acid; and

at least one of the first and the second oligomeric compounds comprises at least one modified nucleoside having enhanced or decreased affinity for the complementary nucleoside in  
10 the composition or between the first oligomeric compound and a nucleic acid target; or

one of the first and the second oligomeric compounds comprises at least one modified nucleoside having enhanced affinity for the complementary nucleoside in the composition or between the first oligomeric compound and a nucleic acid target and one of the first and the second oligomeric compounds comprises at least one modified nucleoside having decreased  
15 affinity for the complementary nucleoside in the composition or between the first oligomeric compound and a nucleic acid target.

2. The composition of claim 1 wherein the first oligomeric compound comprises at least one modified nucleoside having enhanced affinity for the complementary nucleoside in the  
20 composition or between the first oligomeric compound and a nucleic acid target and either the first oligomeric compound or second oligomeric compound comprises at least one modified nucleoside having a decreased affinity for the complementary nucleoside in the composition or between the first oligomeric compound and a nucleic acid target.

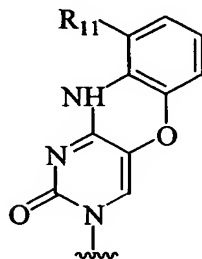
25 3. The composition of claim 1 wherein the first oligomeric compound comprises at least one modified nucleoside having a decreased affinity for the complementary nucleoside in the composition or between the first oligomeric compound and a nucleic acid target, and the second oligomeric compound comprises at least one modified nucleotide having an enhanced affinity for the complementary nucleotide in the first oligomeric compound compared to the affinity of an  
30 unmodified nucleotide.

4. The composition of claim 1 wherein the second oligomeric compound comprises at least one modified nucleotide having an enhanced affinity for the complementary nucleotide in the first oligomeric compound compared to the affinity of an unmodified nucleotide, and

wherein the second oligomeric compound also comprises at least one modified nucleotide having a decreased affinity for the complementary nucleotide in the first oligomeric compound compared to the affinity of an unmodified nucleotide.

- 5 5. The composition of claim 1 wherein the at least one modified nucleotide that comprises an enhanced affinity is a nucleotide comprising a nucleotide base modification.
6. The composition of claim 5 wherein the nucleotide base modification comprises a pyrimidine nucleotide comprising a modification at the 2, 4, 5 or 6 position of the pyrimidine  
10 nucleotide.
7. The composition of claim 6 wherein the pyrimidine nucleotide comprises a modification at the 2 or 5 position of the pyrimidine nucleotide.
- 15 8. The composition of claim 6 wherein the nucleotide base modification comprises a 2-thio U nucleotide substitution for U nucleotide or 2-thio C nucleotide substitution for a C nucleotide.
9. The composition of claim 6 wherein the nucleotide base modification comprises a 5-  
20 alkyl, 5-alkenyl, or 5-alkynyl U substitution for a U nucleotide or 5-alkyl, 5-alkenyl, or 5-alkynyl C substitution for a C nucleotide.
10. The composition of claim 6 wherein the nucleotide base modification comprises a 5-methyl U, 5-methyl C, 5-propynyl U, or 5-propynyl C nucleotide.  
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11. The composition of claim 5 wherein the nucleotide base modification comprises a pyrimidine nucleotide having a modification, wherein the pyrimidine nucleotide is incorporated as one ring of a multiple ring heterocycle.
- 30 12. The composition of claim 11 wherein the multiple ring heterocycle further comprises a phenoxazine moiety.
13. The composition of claim 12 wherein the multiple ring heterocycle comprises the formula:

- 112 -



wherein:

R<sub>11</sub> is (CH<sub>3</sub>)<sub>2</sub>N-(CH<sub>2</sub>)<sub>2</sub>-O-; H<sub>2</sub>N-(CH<sub>2</sub>)<sub>3</sub>-; Ph-CH<sub>2</sub>-O-C(=O)-N(H)-(CH<sub>2</sub>)<sub>3</sub>-; H<sub>2</sub>N-; fluorenyl-CH<sub>2</sub>-O-C(=O)-N(H)-(CH<sub>2</sub>)<sub>3</sub>-; phthalimidyl-CH<sub>2</sub>-O-C(=O)-N(H)-(CH<sub>2</sub>)<sub>3</sub>-; Ph-CH<sub>2</sub>-O-C(=O)-N(H)-(CH<sub>2</sub>)<sub>2</sub>-O-; 5 Ph-CH<sub>2</sub>-O-C(=O)-N(H)-(CH<sub>2</sub>)<sub>3</sub>-O-; (CH<sub>3</sub>)<sub>2</sub>N-N(H)-(CH<sub>2</sub>)<sub>2</sub>-O-; fluorenyl-CH<sub>2</sub>-O-C(=O)-N(H)-(CH<sub>2</sub>)<sub>2</sub>-O-; fluorenyl-CH<sub>2</sub>-O-C(=O)-N(H)-(CH<sub>2</sub>)<sub>3</sub>-O-; H<sub>2</sub>N-(CH<sub>2</sub>)<sub>2</sub>-O-CH<sub>2</sub>-; N<sub>3</sub>-(CH<sub>2</sub>)<sub>2</sub>-O-CH<sub>2</sub>-; H<sub>2</sub>N-(CH<sub>2</sub>)<sub>2</sub>-O-, or NH<sub>2</sub>C(=NH)NH-.

14. The composition of claim 5 wherein the nucleotide base modification comprises a purine nucleotide comprising a modification at the 1, 2, 3, 6, 7 or 8 position of the purine nucleotide.

15. The composition of claim 14 wherein the nucleotide base modification comprises a purine nucleotide comprising a modification at the 2, 6 or 7 positions of the purine nucleotide.

16. The composition of claim 14 wherein the nucleotide base modification comprises a 7-deaza-7-alkyl, 7-deaza-7-alkenyl, or 7-deaza-7-alkynyl A substitution for a A nucleotide or 7-deaza-7-alkyl, 7-deaza-7-alkenyl, or 7-deaza-7-alkynyl G substitution for a G nucleotide.

17. The composition of claim 14 wherein the nucleotide base modification comprises a 2,6-diamino purine substitution for an A nucleotide.

18. The composition of claim 1 wherein the at least one modified nucleotide that comprises an enhanced affinity is a nucleotide comprising a nucleotide sugar modification.

19. The composition of claim 18 wherein the nucleotide sugar modification comprise 2'-F, 2'-MOE, 2'-O-methyl, 2'-O-alkyl, 2'-O-alkenyl, 2'-O-alkynyl, 2'-S-alkyl, 2'-S-alkenyl, 2'-S-alkynyl, 2'-amino, 2'-azido, or 2'-allyl.

20. The composition of claim 1 wherein the at least one modified nucleotide that comprises an enhanced affinity is a nucleotide comprising a modified internucleotide linkage.

21. The composition of claim 20 wherein the modified internucleotide linkage comprises a  
5 stabilizing internucleotide linkage.

22. The composition of claim 21 wherein the stabilizing internucleotide linkage comprises a 3'-deoxy-3'-aminophosphoramidate, 3'-deoxy-3'-methylene phosphonate, 3'-deoxy-3'-aminothiophosphoramidate, acetal, thioacetal, amide-3 and amide-4, MMI, hydrazine, or  
10 morpholino.

23. The composition of claim 1 wherein the at least one modified nucleotide that comprises a decreased affinity is a nucleotide comprising a nucleotide base modification.

15 24. The composition of claim 23 wherein the nucleotide base modification comprises an inosine nucleotide or a purine ribofuranosyl nucleotide.

25. The composition of claim 1 wherein the at least one modified nucleotide that comprises a decreased affinity is a nucleotide comprising a nucleotide sugar modification.

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26. The composition of claim 25 wherein the sugar modification comprises a 2'-endo sugar.

27. The composition of claim 1 wherein the at least one modified nucleotide that comprises a decreased affinity is a nucleotide comprising at least one modified internucleotide linkage.

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28. The composition of claim 27 wherein the modified internucleotide linkage comprises a destabilizing internucleotide linkage.

29. The composition of claim 28 wherein the destabilizing internucleotide linkage  
30 comprises a phosphorothioate, phosphorodithioate, phosphoramidate, phosphotriester, or alkyl phosphonate internucleotide linkage.

30. The composition of claim 5 or claim 23 wherein the nucleotide base modification comprises a 2'-substituent group which is, independently, F, -O-CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>3</sub>, -O-C<sub>1</sub>-C<sub>12</sub>

alkyl, -O-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>2</sub>-O-N(R<sub>1</sub>)<sub>2</sub>, -O-CH<sub>2</sub>C(=O)-N(R<sub>1</sub>)<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>2</sub>-O-(CH<sub>2</sub>)<sub>2</sub>-N(R<sub>1</sub>)<sub>2</sub>, -O-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-NHR<sub>1</sub>, -O-CF<sub>3</sub>, -N<sub>3</sub>, -O-CH<sub>2</sub>-CH=CH<sub>2</sub>, -NHCOR<sub>1</sub>, -NH<sub>2</sub>, -NHR<sub>1</sub>, -N(R<sub>1</sub>)<sub>2</sub>, -SH, -SR<sub>1</sub>, -N(H)OH, -N(H)OR<sub>1</sub>, -N(R<sub>1</sub>)OH, -N(R<sub>1</sub>)OR<sub>1</sub> or -O-CH<sub>2</sub>-N(H)-C(=NR<sub>1</sub>)(N(R<sub>1</sub>)<sub>2</sub>);

5            wherein each R<sub>1</sub> is, independently, H, C<sub>1</sub>-C<sub>12</sub> alkyl, a protecting group, or substituted or unsubstituted C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>2</sub>-C<sub>12</sub> alkenyl, or C<sub>2</sub>-C<sub>12</sub> alkynyl, wherein the substituent groups are halogen, hydroxyl, amino, azido, cyano, haloalkyl, alkenyl, alkoxy, thioalkoxy, haloalkoxy, or aryl.

10 31.      The composition of claim 30 wherein each of the 2'-substituent groups is, independently, -F, -O-CH<sub>3</sub>, -O-CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>3</sub>, -O-CH<sub>2</sub>-CH=CH<sub>2</sub>, -O-CF<sub>3</sub>, N<sub>3</sub>, NH<sub>2</sub>, NHOH, -O-(CH<sub>2</sub>)<sub>2</sub>-O-N(R<sub>1</sub>)<sub>2</sub>, -O-CH<sub>2</sub>C(O)-N(R<sub>1</sub>)<sub>2</sub>, -O-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>2</sub>-O-(CH<sub>2</sub>)<sub>2</sub>-N(R<sub>1</sub>)<sub>2</sub> or -O-CH<sub>2</sub>-N(H)-C(=NR<sub>1</sub>)(N(R<sub>1</sub>)<sub>2</sub>);

            wherein each R<sub>1</sub> is, independently, H, C<sub>1</sub>-C<sub>12</sub> alkyl, a protecting group, or substituted or  
15 unsubstituted C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>2</sub>-C<sub>12</sub> alkenyl, or C<sub>2</sub>-C<sub>12</sub> alkynyl, wherein the substituent groups are halogen, hydroxyl, amino, azido, cyano, haloalkyl, alkenyl, alkoxy, thioalkoxy, haloalkoxy, or aryl.

32.      The composition of claim 31 wherein each of the 2'-substituent groups is,  
20 independently, -F, -O-CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>3</sub>, -O-CH<sub>3</sub>, -O-CH<sub>2</sub>-CH=CH<sub>2</sub>, -O-CF<sub>3</sub> or -O-CH<sub>2</sub>-CH-CH<sub>2</sub>-NH(R<sub>j</sub>) where R<sub>j</sub> is H or C<sub>1</sub>-C<sub>10</sub> alkyl.

33.      The composition of claim 32 wherein each of the 2'-substituent groups is,  
independently, F, -O-CH<sub>3</sub>, -O-CF<sub>3</sub>, or -O-CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>3</sub>.

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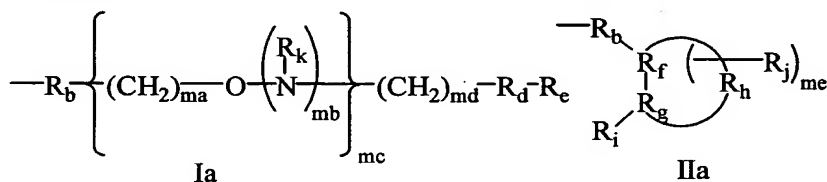
34.      The composition of claim 5 or claim 23 wherein at least one modified nucleotide base is a locked nucleic acid (LNA).

35.      The composition of claim 18 or claim 25 wherein the nucleotide sugar modification is,  
30 independently, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>20</sub> alkenyl, C<sub>2</sub>-C<sub>20</sub> alkynyl, C<sub>5</sub>-C<sub>20</sub> aryl, -O-alkyl, -O-alkenyl, -O-alkynyl, -O-alkylamino, -O-alkylalkoxy, -O-alkylaminoalkyl, -O-alkyl imidazole, -OH, -SH, -S-alkyl, -S-alkenyl, -S-alkynyl, -N(H)-alkyl, -N(H)-alkenyl, -N(H)-alkynyl, -N(alkyl)<sub>2</sub>, -O-aryl, -S-aryl, -NH-aryl, -O-aralkyl, -S-aralkyl, -N(H)-aralkyl, phthalimido (attached at N), halogen, amino, keto (-C(=O)-Ra), carboxyl (-C(=O)OH), nitro (-NO<sub>2</sub>), nitroso (-N=O), cyano (-CN),

trifluoromethyl (-CF<sub>3</sub>), trifluoromethoxy (-O-CF<sub>3</sub>), imidazole, azido (-N<sub>3</sub>), hydrazino (-N(H)-NH<sub>2</sub>), aminooxy (-O-NH<sub>2</sub>), isocyanato (-N=C=O), sulfoxide (-S(=O)-R<sub>a</sub>), sulfone (-S(=O)<sub>2</sub>-R<sub>a</sub>), disulfide (-S-S-R<sub>a</sub>), silyl, heterocyclyl, carbocyclyl, an intercalator, a reporter group, a conjugate group, polyamine, polyamide, polyalkylene glycol, or a polyether of the formula (-O-alkyl)<sub>ma</sub>;

- 5 wherein each R<sub>a</sub> is, independently, hydrogen, a protecting group, or substituted or unsubstituted alkyl, alkenyl, or alkynyl, wherein the substituent groups are haloalkyl, alkenyl, alkoxy, thioalkoxy, haloalkoxy, aryl, halogen, hydroxyl, amino, azido, carboxy, cyano, nitro, mercapto, a sulfide group, a sulfonyl group, or a sulfoxide group;

or each sugar substituent group has one of formula Ia or IIa:



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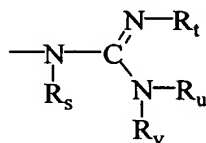
wherein:

R<sub>b</sub> is O, S or NH;

R<sub>d</sub> is a single bond, O, S or C(=O);

R<sub>e</sub> is C<sub>1</sub>-C<sub>10</sub> alkyl, N(R<sub>k</sub>)(R<sub>m</sub>), N(R<sub>k</sub>)(R<sub>n</sub>), N=C(R<sub>p</sub>)(R<sub>q</sub>), N=C(R<sub>p</sub>)(R<sub>r</sub>) or has formula

- 15 IIIa;



IIIa

R<sub>p</sub> and R<sub>q</sub> are each, independently, hydrogen or C<sub>1</sub>-C<sub>10</sub> alkyl;

R<sub>r</sub> is -R<sub>x</sub>-R<sub>y</sub>;

- each R<sub>s</sub>, R<sub>t</sub>, R<sub>u</sub> and R<sub>v</sub> is, independently, hydrogen, C(O)R<sub>w</sub>, substituted or unsubstituted C<sub>1</sub>-C<sub>10</sub> alkyl, substituted or unsubstituted C<sub>2</sub>-C<sub>10</sub> alkenyl, substituted or unsubstituted C<sub>2</sub>-C<sub>10</sub> alkynyl, alkylsulfonyl, arylsulfonyl, a chemical functional group, or a conjugate group, wherein the substituent groups are hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl, or alkynyl;

- or, optionally, R<sub>u</sub> and R<sub>v</sub>, together form a phthalimido moiety with the nitrogen atom to which they are attached;
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each  $R_w$  is, independently, substituted or unsubstituted  $C_1$ - $C_{10}$  alkyl, trifluoromethyl, cyanoethoxy, methoxy, ethoxy, t-butoxy, allyloxy, 9-fluorenylmethoxy, 2-(trimethylsilyl)-ethoxy, 2,2,2-trichloroethoxy, benzyloxy, butyryl, iso-butyryl, phenyl, or aryl;

$R_x$  is a bond or a linking moiety;

5  $R_y$  is a chemical functional group, a conjugate group or a solid support medium;

$R_k$  is hydrogen, a nitrogen protecting group or  $-R_x-R_y$ ;

each  $R_m$  and  $R_n$  is, independently, H, a nitrogen protecting group, substituted or unsubstituted  $C_1$ - $C_{10}$  alkyl, substituted or unsubstituted  $C_2$ - $C_{10}$  alkenyl, substituted or unsubstituted  $C_2$ - $C_{10}$  alkynyl, wherein the substituent groups are hydroxyl, amino, alkoxy, 10 carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl, alkynyl,  $NH_3^+$ ,  $N(R_u)(R_v)$ , guanidine, or acyl where the acyl is an acid amide or an ester;

or  $R_m$  and  $R_n$ , together, are a nitrogen protecting group, are joined in a ring structure that optionally includes an additional heteroatom selected from N and O, or are a chemical functional group;

15  $R_i$  is  $OR_z$ ,  $SR_z$ , or  $N(R_z)_2$ ;

each  $R_z$  is, independently, H,  $C_1$ - $C_8$  alkyl,  $C_1$ - $C_8$  haloalkyl,  $C(=NH)N(H)R_u$ ,  $C(=O)N(H)R_u$  or  $OC(=O)N(H)R_u$ ;

$R_f$ ,  $R_g$  and  $R_h$  comprise a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 heteroatoms wherein the heteroatoms are 20 oxygen, nitrogen, or sulfur and wherein the ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic;

$R_j$  is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms,  $N(R_k)(R_m)$   $OR_k$ , halo,  $SR_k$  or CN;

25  $ma$  is 1 to about 10;

each  $mb$  is, independently, 0 or 1;

$mc$  is 0 or an integer from 1 to 10;

$md$  is an integer from 1 to 10;

$me$  is from 0, 1 or 2; and

30 provided that when  $mc$  is 0,  $md$  is greater than 1.

36. The composition of claim 1 wherein each of the first and second oligomeric compounds comprises from about 8 to about 80 nucleobases.

37. The composition of claim 1 wherein each of the first and second oligomeric compounds comprises from about 10 to about 50 nucleobases.
38. The composition of claim 1 wherein each of the first and second oligomeric compounds  
5 comprises from about 12 to about 30 nucleobases.
39. The composition of claim 1 wherein each of the first and second oligomeric compounds comprises from about 12 to about 24 nucleobases.
- 10 40. The composition of claim 1 wherein each of the first and second oligomeric compounds comprises from about 19 to about 23 nucleobases.
41. A method of inhibiting the expression of a nucleic acid molecule encoding a target protein in a cell, tissue, or animal comprising contacting the cell, tissue, or animal with the  
15 composition of claim 1, wherein the first oligomeric compound specifically hybridizes with the nucleic acid molecule encoding the target protein and inhibits the expression of the target protein.
42. A method of screening for a modulator of a target, the method comprising:  
20 contacting a target segment of a nucleic acid molecule encoding the target with one or more modulator candidates selected from the compositions of claim 1; and  
identifying one or more modulators of the target expression which modulate the expression of the target.
- 25 43. The method of claim 42 wherein the modulator of the target expression comprises an oligonucleotide, an antisense oligonucleotide, a DNA oligonucleotide, an RNA oligonucleotide, an RNA oligonucleotide having at least a portion of the RNA oligonucleotide capable of hybridizing with RNA to form an oligonucleotide-RNA duplex, or a chimeric oligonucleotide.
- 30 44. A kit or assay device comprising the composition of claim 1.
45. A method of treating an animal having a disease or condition associated with a target protein comprising administering to the animal a therapeutically or prophylactically effective amount of the composition of claim 1 so that expression of the target is inhibited.



46. A method of reducing the expression of a gene in a biological system expressing the gene comprising:

providing a composition of claim 1; and

5 contacting the biological system with the composition under conditions effective to reduce the expression of the gene, wherein the composition comprises at least one of the first and second oligomeric compounds is an RNA oligomer.

47. The composition of claim 1 wherein the first and second oligomeric compounds are a complementary pair of siRNA oligonucleotides.

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48. The composition of claim 1 wherein the first oligomeric compound is an antisense oligonucleotide.

49. The composition of claim 1 wherein the second oligomeric compound is a sense  
15 oligonucleotide.

50. A composition comprising the composition of claim 1 and at least one protein comprising at least a portion of an RNA-induced silencing complex (RISC).